**REQUEST FOR PROPOSAL - SPECIFICATIONS**
***TOTAL EXPOSURE PILOT STUDY***

**Study Objective:**

The *objective* of the present pilot study is to establish the validity of the design concepts (e.g, feasibility and precision of analytical methods for biomarkers, sample handling and stability, data acquisition by questionnaire) to be used in the subsequent Total Exposure Study. In particular the study should determine the intra-individual variability of each estimate of smoke constituent uptake as a basis for the design of the Total Exposure Study. The results and evaluations of the pilot study should be complete and made available to Philip Morris within the year 2000.

**Introduction:**

The Total Exposure Study (main study) is intended to provide a 'baseline' estimate of the exposure of the U.S. population of adult cigarette smokers to selected smoke constituents in both the gas/vapor and the particle phase of cigarette smoke. It should provide reference information and methodological insights for a subsequent series of studies in adult smokers. These later studies could investigate the effect of changes of cigarette design, which are aimed at harm reduction, on exposure to smoke constituents.

The *primary objective* of the Total Exposure Study is to determine the exposure of the U. S. population of adult cigarette smokers to selected constituents of whole cigarette smoke based on suitable biomarker(s) and to publish results by 12/31/2001. The *secondary objective* is to investigate whether the smoke exposure of US adult cigarette smokers differs for 4 segments of FTC tar delivery covering the range from 1 to 20 mg tar. In addition, selected biomarkers of potential health effects/susceptibility will be explored for use in population studies, and biological samples will be collected and stored for later determinations of biomarkers of health effects relevant to potentially reduced harm of cigarette products to adult smokers.

The Total Exposure Study seeks to estimate the exposure of populations and to test a research hypothesis. The population estimate is the frequency distribution of exposure to specific smoke constituents (as measured by biomarkers) for U.S. adult smokers and non-smokers. The estimates obtained for non-smokers will provide a measure of the background level of exposure. The research hypothesis is to test if the smoke exposure of adult smokers differs by tar groupings of the cigarettes they regularly smoke i.e., <3.0, 3.0-6.9, 7.0-11.9, and 12.0-20.0 mg tar (FTC measures) per cigarette for each smoke constituent.



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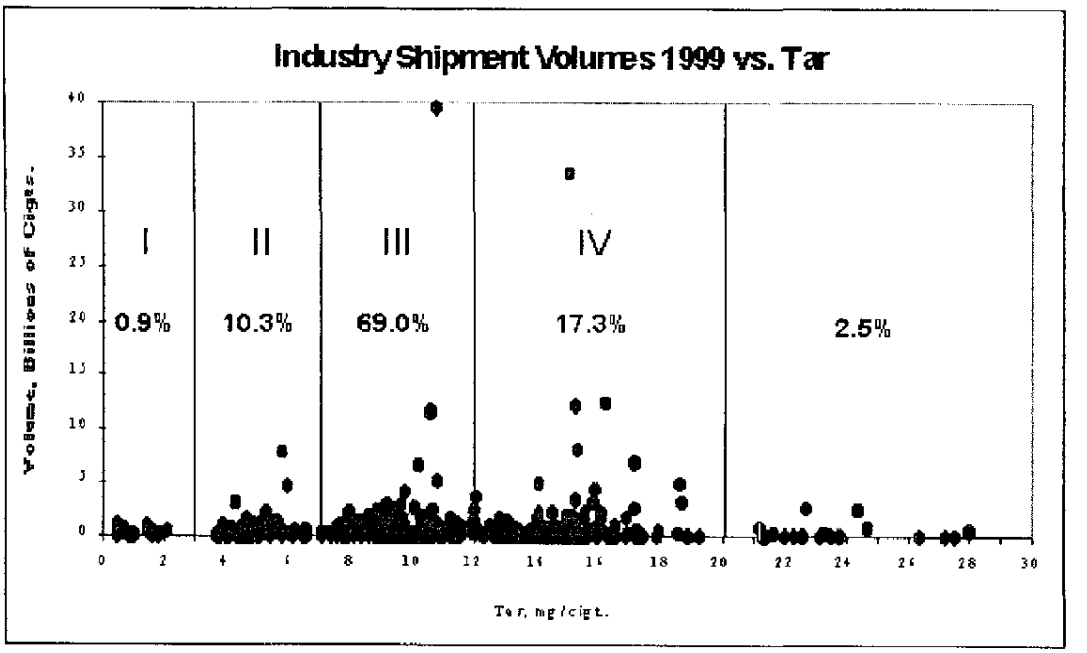


Ref.: Tobacco Institute Testing Laboratory

The Total Exposure Study will also explore the feasibility of selected biomarkers of susceptibility/potential health effects and collect and store biological samples for exploratory analyses of biomarkers of health effects relevant to determine reduced harm of cigarette products in smokers after the completion of this study.

The design outlined below represents the design of the pilot study. The current design draft for the Total Exposure Study is added as an Appendix for reference purposes.

**Study population:**

The study population will comprise of adult smokers currently smoking cigarette products with 3.0-6.9 mg tar (FTC) delivery per cigarette and non-tobacco-users. Adult current smokers are defined by reporting to smoke regularly at least 1 cigarette of a specified brand per day for at least 1 year.

The study population in the pilot study does not need to be representative of the age, gender, ethnic, and socioeconomic distribution of the U.S. adult cigarette smoking population, but should represent a randomly selected group of smokers. The brands of cigarettes smoked should fall into the specified tar ranges but there is not any selection



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for cigarette manufacturers, cigarette design and composition (e.g. filter or unfiltered, mentholated or not mentholated).

Non-tobacco-users are defined as adult subjects not smoking at all or less than 1 cigarette/day for the last year or using any nicotine-containing products such as snuff, chewing tobacco, patches, sprays during and 1 month before the sample collections for this study. Their reported absence of active nicotine uptake will be verified by determination of urinary cotinine. Persons with urinary cotinine exceeding 50 ug/l will be excluded from this group.

**Sample size and grouping:**

Sixty adult 3-7 mg-smokers, and 60 adult non-tobacco-users (control group) each. Each group will contain 30 males and 30 females. The total number of subjects for the adult smoker's groups will therefore be 120.

Dropouts will be replaced.

**Subject exclusion criteria:**

Subjects who report the following characteristics will be excluded from the test sample:

- Smoke a cigarette brand with tar delivery per cigarette different than the specified range (3-7 mg/cig.);
- Have switched to a new brand during the last month prior to the sample collection;
- Use of other cigarette brand(s) at a level >10%of the consumption of their preferred cigarette brand during the last month before sample collection;
- Use of any nicotine-containing product other than manufactured cigarettes;
- Diseases (reported as diagnosed plus confirmation of healthy status by X-ray, routine hematology, pulmonary function test, and ECG) which could interfere with the measured health effect surrogates such as all currently diagnosed cancers, diabetes, coronary heart disease, hypertension, stroke, heart infarction, bronchitis (acute and chronic), emphysema, asthma, renal dysfunction, hyperlipidemia;
- Pregnant women;
- Nursing women;
- Persons of less than 21 years of age (age verification required by copy of government issued identification);
- Subjects exceeding 50 ug cotinine/l urine for the non-tobacco user group;
- Subjects where reported number of cigarettes smoked and butts collected differ by more than 10%;



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**Sample collection:**

Either random sample collection based on 'Population kinetics' approach (non-linear mixed modeling) acc. to FDA procedures or strictly specified procedure, both with reporting of at least the time of day.

- Venous blood (3 samples per subject at specified time of day on 3 subsequent days; 15 ml each);
- Exhalate (e.g. Tedlar bag; 3 samples per subject at specified time of day on 3 subsequent days, 500 ml each);
- Induced sputum (3 samples per subject at specified time of day on 3 subsequent days);
- 24-h urine (3 24-h periods per subject at specified time of day on 3 subsequent days; collection of each urine delivery separately, recording of time of collection; storage below room temperature before transfer to the clinical facility);
- All cigarette butts of all cigarettes smoked during the days of urine sample collection.
- All packs from which smoked cigarettes were drawn during days of sample collection.

**Biomarkers selected:**

To minimize invasive sampling requirements and in accordance with NRC selection criteria as proposed by Benowitz the following biomarkers for exposure were selected:



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| BIOMARKER | SAMPLE MATERIAL | SMOKE CONSTITUENT | SMOKE PHASE (b) |
|---|---|---|---|
| Acetonitrile | Exhalate and urine | Acetonitrile | GVP |
| Carbon monoxide | Exhalate | Carbon monoxide | GVP |
| Carboxy-hemoglobin | Blood | Carbon monoxide | GVP |
| Hb adducts of 3- and 4-aminobiphenyl | Blood | 3- and 4-aminobiphenyl | PP |
| Nicotine and nicotine metabolites (a) | 24-hr urine | Nicotine | PP |
| NNAL and NNAL-glucuronide | 24-hr urine | NNK | PP |
| Cadmium | Blood | Cadmium | PP |

(a) cotinine, 3-hydroxycotinine, nicotine glucuronide, cotinine glucuronide, 3-hydroxycotinine glucuronide,
(b) GVP: gas-vapor phase; PP: particle phase

In addition the following biomarkers of susceptibility/potential health effects will be analyzed (preliminary selection) as a basis for future studies (exploratory):

| BIOMARKER | SAMPLE MATERIAL | RELATED HEALTH ENDPOINT |
|---|---|---|
| Thromboxane B2 | 24-hr urine | Atherosclerosis |
| HDL, LDL | blood | Atherosclerosis |
| Isoprostanes | 24-hr urine | Lipid peroxidation |
| Malondialdehyde | Blood | Oxidative stress |
| Fibrinogen | blood | Cardiovascular disease |

**Storage of sample materials for future analyses:**

Blood (serum or plasma), sputum, and urine samples will be stored below -18 degrees centigrade for future (exploratory) studies with determinations of biomarkers of health effects relevant to determine reduced harm of cigarette products to adult smokers. Consent will be sought from subjects to allow testing for future biomarkers of exposure, potential health effects, with the proviso that reports of such results will not be shared with subjects nor contain subject identification.



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**Analytical methods for biomarkers:**

Methods with adequate sensitivity, reproducibility, and selectivity are used. Analytical determinations should be based on intra-laboratory validated methods and is encouraged to comply with clinical standards (CLIA) or GLP (compliance will be required in the main study.

**Questionnaire evaluations:**

The objectives for the questionnaire are:

- To check for exclusion criteria;
- To allow for regression analyses and analyses of 'outliers';
- To evaluate aspects of smoking behavior.

By interviewing all subjects with the help of trained staff and using structured questionnaires the following information will be collected from all study subjects:

- Demographics (age, gender, ethnic characterization, marital status, education, socioeconomic status, geographic location);
- Health status and history;
- Exposure to cigarette smoke by active smoking, brands smoked (incl. Information on "tar" and nicotine yield (FTC listing), mentholation, filter type, circumference, and cigarette length) for a specified timeframe, daily tobacco consumption;
- Smoking activities during 2 days prior to and during day of urine sample collection (diary);
- Smoking characteristics (e.g., inhalation/puffing);
- Exposure to ETS (strength and duration);
- Occupational exposures (in particular those that could interfere with the selected biomarkers);
- Diet characteristics incl. alcohol consumption;
- Hobbies
- Home heating systems;
- Exposure to car exhaust
- Medication/supplementation such as herbal or vitamin supplements (if at least 3 days/week), chemotherapeutics, acetylsalicylic acid-containing drugs, cyclooxygenase inhibitors;
- Start of last menstrual period (women);
- Use of non-tobacco nicotine products;
- Physical activity.

**Analyses**:



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In addition to the biomarkers of exposure and susceptibility/potential health effects (see above) creatinine in urine will be determined.

**Study organization:**

A *contract research organization (CRO)* will be engaged to manage, execute or subcontract and oversee the following tasks:

- Advise Philip Morris on potential modification of its study design in the context of the objectives of the pilot study and the Total Exposure Study.
- Cooperate with an external primary investigator (recognized external expert in an area relevant for this study, experienced in managing human studies with bio-analytical focus)
- Establishment (e.g., design/print/ship/review) of a detailed study protocol;
- Preparation/Participation of meeting with Philip Morris and collaborators/ subcontractors;
- Ethical committee consent;
- Sample population selection and recruitment;
- Payment administration to subjects and subcontractors;
- Informed Consent declarations (e.g., preparation/execution/documentation) by study subjects;
- Individual subject documentation (e.g., design/print/translation/shipment/review of case report form (CRF));
- Training of interviewers;
- Questionnaire and diaries evaluation;
- Site identification/selection;
- Development of randomized schedule;
- Collection of biological samples;
- Transportation of collected samples to analytical laboratory and sample storage;
- Selection of analytical laboratory(ies) (requires consent by Philip Morris);
- Biomarker analyses;
- Ensuring subject compliance with study protocol and sample collection protocols;
- Validation of reported smoking (number of cigarettes and brand) against collected cigarette butts;
- Full regulatory compliance including GCP (FDA and ICH regulations) and GLP compliance (if available) and collection/review of regulatory documents (e.g. local IRBs, central IRB);
- Data management planning meeting;
- Development of data management manual;
- Design of database;
- Development of program data edit specifications;
- Review of questionnaires/diaries against exclusion criteria;
- CRF tracking by specified method;
- Data entry/editing/verification;



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- Generation/resolution of edits/queries;
- Imaging;
- Data coding;
- Incorporation of analytical data into database;
- Progress reporting;
- Database transfer (e.g., SAS);
- Development of statistical analysis plan;
- Data review meeting;
- Statistical evaluations;
- Final statistical report;
- Writing/editing/shipment/copying of final integrated report(s).

The *scientific advisor* (if nominated) will:

- Advise Philip Morris on the design, execution, evaluation, and reporting of the study
- Contribute to the development of the protocol for the pilot study;
- Ensure the study quality.

*Philip Morris* will:

- Provide a study design for the pilot and Total Exposure Study;
- Support definition of demographics of US smoker population;
- Select or suggest a CRO;
- Select and contract with the scientific advisor
- Select additional quality assurance oversight functions;
- Provide adequate funding;
- Provide other study materials and support as required and agreed.

END OF DESIGN



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